

## STN SEARCH

10/664,421

FILE 'HOME' ENTERED AT 07:25:17 ON 23 MAY 2006

=> file medline, Caplus  
=> s benzimidazol and kinase and inhibitor  
L1 14 FILE MEDLINE  
L2 158 FILE CAPLUS

## TOTAL FOR ALL FILES

L3 172 BENZIMIDAZOL AND KINASE AND INHIBITOR

=> s l3 not 2003-2006/py  
L4 7 FILE MEDLINE  
L5 8 FILE CAPLUS

## TOTAL FOR ALL FILES

L6 15 L3 NOT 2003-2006/PY

=> dup rem l6  
PROCESSING COMPLETED FOR L6  
L7 10 DUP REM L6 (5 DUPLICATES REMOVED)

=> d ibib abs 1-10

L7 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:790223 CAPLUS Full-text

DOCUMENT NUMBER: 137:310915

TITLE: Preparation of benzimidazole and imidazopyridine derivatives as angiogenesis inhibitors

INVENTOR(S): Bilodeau, Mark T.; Hungate, Randall W.; Cunningham, April M.; Koester, Timothy J.

PATENT ASSIGNEE(S): Merck &amp; Co., Inc., USA

SOURCE: U.S., 19 pp., Cont.-in-part of U.S. Ser. No. 143,881, abandoned.

CODEN: USXXAM

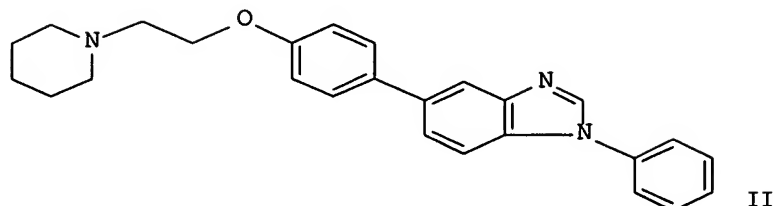
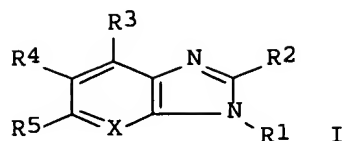
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

## PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6465484	B1	20021015	US 2001-786004	20010228
WO 2000012089	A1	20000309	WO 1999-US5297	19990311
W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 1997-60151P	P 19970926
			US 1998-143881	B2 19980831
			WO 1999-US5297	W 19990311
OTHER SOURCE(S):			MARPAT 137:310915	
GI				



AB Title compds. I [X = N; R1 = aryl, heterocyclyl, heteroaryl; R2-3, R5 = H, alkyl; R4 = H, alkyl] were prepared. For instance, 1-Bromo-4-fluoro-3-nitrobenzene was reacted with aniline (NMP, i-Pr2NEt, 120°, 14 h), the product coupled to 4-methoxyboronic acid (dioxane/water, Na2CO3, [PPh3]4Pd, 80°, 14 h) and the biaryl reduced (EtOH/HOAc, Pd/C-H2, 2 h) and the resulting intermediate treated with (MeO)3CH at 120° for 30 min to afford 1-phenyl-5-(4-methoxyphenyl)benzimidazole. This was demethylated (CH3CN/CH2Cl2, AlCl3, NaI, reflux, 44 h) and the resulting phenol reacted with 1-(2-chloroethyl)piperidine hydrochloride (DMF, Cs2CO3, 50°) to give II. Compds. of the invention inhibit VEGF-stimulated mitogenesis of human vascular endothelial cells in culture with IC50 values between 150-650 nM. I are useful for the treatment of tyrosine kinase-dependent diseases/conditions such as angiogenesis, cancer, atherosclerosis, diabetic retinopathy or autoimmune diseases.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 10 MEDLINE on STN DUPLICATE 1  
 ACCESSION NUMBER: 2002690151 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 12451114  
 TITLE: Prolonged activation of Ca2+-activated K+ current contributes to the long-lasting refractory period of Aplysia bag cell neurons.  
 AUTHOR: Zhang Yalan; Magoski Neil S; Kaczmarek Leonard K  
 CORPORATE SOURCE: Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06520, USA.  
 CONTRACT NUMBER: NS 18492 (NINDS)  
 SOURCE: The Journal of neuroscience : the official journal of the Society for Neuroscience, (2002 Dec 1) Vol. 22, No. 23, pp. 10134-41.  
 Journal code: 8102140. E-ISSN: 1529-2401.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200212  
 ENTRY DATE: Entered STN: 14 Dec 2002  
 Last Updated on STN: 27 Dec 2002  
 Entered Medline: 23 Dec 2002

AB Stimulation of the bag cell neurons of Aplysia activates several biochemical pathways, including protein kinase C (PKC), and alters their excitability for many hours. After an approximately 30 min afterdischarge, these neurons enter an approximately 18 hr inhibited state during which additional stimulation fails to evoke discharges. In vivo, this refractory period limits the frequency of reproductive behaviors associated with egg laying. We have now examined the role of Ca2+-activated K+ (BK) currents in the refractory period. Outward currents gated by both intracellular Ca2+ and depolarization, with pharmacological characteristics of BK currents, were recorded in isolated bag cell neurons. These currents were enhanced by the BK channel activators phloretin and 1,3-

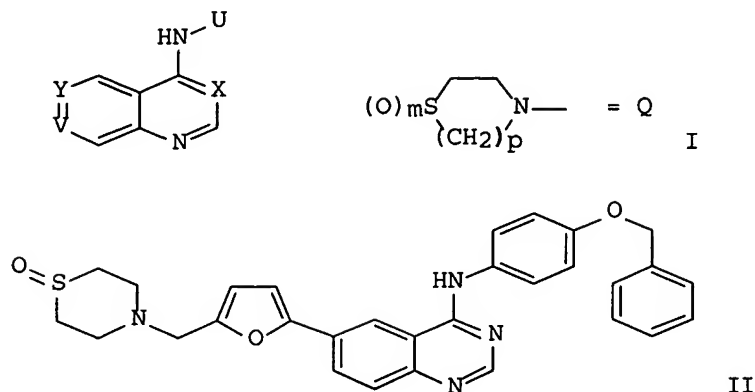
dihydro-1-[2-hydroxy-5-(trifluoro-methyl)phenyl]-5-trifluoromethyl-2H-benzimidazol-2-one and inhibited by the BK blocker paxilline. The BK component of K<sup>+</sup> current was enhanced by 12-O-tetradecanoyl-phorbol-13-acetate, an activator of PKC, and this effect was blocked by sphinganine and PKC(19-36), inhibitors of PKC in bag cell neurons. To test whether the BK current is altered during the refractory period, intact clusters were stimulated to afterdischarge, and neurons were isolated after the clusters had entered the refractory period. Compared with unstimulated cells, current density was almost doubled in refractory neurons. This increase in current was inhibited by preincubating clusters in sphinganine. Treatment of refractory clusters with paxilline significantly restored the ability of stimulation to evoke afterdischarges. Conversely, application of phloretin to previously unstimulated clusters inhibited the onset of afterdischarges. These results indicate that a prolonged increase in BK channel activity contributes to the prolonged refractory period of the bag cell neurons.

L7 ANSWER 3 OF 10 MEDLINE on STN DUPLICATE 2  
 ACCESSION NUMBER: 2002355457 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 12020691  
 TITLE: Cyclic AMP-independent relaxation mediated by  
 beta3-adrenoceptors on guinea pig gastrointestinal.  
 AUTHOR: Horinouchi Takahiro; Koike Katsuo  
 CORPORATE SOURCE: Department of Chemical Pharmacology, Toho University School  
 of Pharmaceutical Sciences, 2-2-1 Miyama, Funabashi, Chiba,  
 Japan.  
 SOURCE: European journal of pharmacology, (2002 May 3) Vol. 442,  
 No. 1-2, pp. 137-46.  
 Journal code: 1254354. ISSN: 0014-2999.  
 PUB. COUNTRY: Netherlands  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200210  
 ENTRY DATE: Entered STN: 9 Jul 2002  
 Last Updated on STN: 10 Oct 2002  
 Entered Medline: 8 Oct 2002

AB In this study, we investigated the signal transduction pathway involved in beta(3)-adrenoceptor-mediated relaxations of guinea pig gastric fundus and duodenum. In the presence of beta1- and beta2-adrenoceptor blockade, the potency (pD2 value) of catecholamines ((-)-isoprenaline, (-)-noradrenaline and (-)-adrenaline) and beta(3)-adrenoceptor agonists ((R\*, R\*)-(+/-)-4-[2-[(2-(3-chlorophenyl)-2-hydroxyethyl)amino]propyl]phenoxy)acetic acid sodium (BRL37344) and (+/-)-[4-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1,3-dihydro-2H-benzimidazol-2-one] hydrochloride ((+/-)-CGP12177A)) to induce relaxation was not affected by the adenylate cyclase inhibitor, 9-(tetrahydro-2-furanyl)-9H-purin-6-amine (SQ-22,536, 100 microM). Catecholamines induced an elevation of cyclic AMP and SQ-22,536 significantly abolished the responses of gastric fundus. However, cyclic AMP levels were unaltered by the beta3-adrenoceptor agonists in gastric fundus and by the five agonists in duodenum. Furthermore, the relaxant responses to catecholamines and to beta3-adrenoceptor agonists were unaffected by the cyclic AMP-dependent protein kinase inhibitor, N-(2-[p-bromocinnamylamino]ethyl)-5-isoquinolinesulfonamide (H-89, 10 microM) in gastric fundus. These results suggest that beta3-adrenoceptor-induced relaxation is mediated through both cyclic AMP-dependent and cyclic AMP-independent pathways in gastric fundus and through a cyclic AMP-independent pathway in duodenum.

L7 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 2000:854415 CAPLUS Full-text  
 DOCUMENT NUMBER: 133:362769  
 TITLE: Preparation of 6-(thiomorpholinomethylfuranyl)-4-quinazolinamines as protein tyrosine kinase inhibitors  
 INVENTOR(S): Carter, Malcolm Clive; Cockerill, George Stuart;  
 Guntrip, Stephen Barry; Lackey, Karen Elizabeth;  
 Smith, Kathryn Jane  
 PATENT ASSIGNEE(S): Glaxo Group Ltd., UK  
 SOURCE: Brit. UK Pat. Appl., 151 pp.  
 CODEN: BAXXDU  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 2345486	A1	20000712	GB 1999-29973	19991217
PRIORITY APPLN. INFO.:			GB 1999-518	A 19990111
			GB 1999-15510	A 19990703
OTHER SOURCE(S):	MARPAT 133:362769			
GI				



AB The title compds. (I) [wherein X = N or CH; V and Y = independently CR<sub>1</sub>, CR<sub>2</sub>, or N; and V ≠ Y; R<sub>1</sub> = Q(CH<sub>2</sub>)<sub>q</sub>Ar; m = 1 or 2; p = 1 or 2; q = 1-4; Ar = (un)substituted Ph, furanyl, thiophenyl, pyrrolyl, or thiazolyl; R<sub>2</sub> = H, halo, OH, alkyl(amino) alkoxy, or dialkylamino; U = (un)substituted Ph, pyridyl, (benz)imidazolyl, (iso)indolyl, (iso)indolinyl, indazolyl, or benzotriazolyl] were prepared as protein tyrosine kinase inhibitors for the treatment of cancer and other disorders mediated by aberrant protein tyrosine kinase activity. For example, II•2HCl was formed in a multi-step sequence involving (1) reaction of 5-(1,3-dioxolan-2-yl)-2-(tributylstannyl)furan with (4-benzyloxyphenyl)(6-bromoquinazolin-4-yl)amine using Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> in dioxane, (2) conversion of the cyclic acetal to the aldehyde with HCl in THF, (3) addition of thiomorpholine-S-oxide in CH<sub>2</sub>Cl<sub>2</sub> and conversion to the HCl salt. I inhibited EGFR and c-erbB-2 tyrosine kinase with IC<sub>50</sub> < 0.10 μM and suppressed cell proliferation against a range of tumor cell lines.

L7 ANSWER 5 OF 10 MEDLINE on STN DUPLICATE 3

ACCESSION NUMBER: 2001043156 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 11011029

TITLE: BRL37344, but not CGP12177, stimulates fuel oxidation by soleus muscle in vitro.

AUTHOR: Board M; Doyle P; Cawthorne M A

CORPORATE SOURCE: Clore Laboratory for Metabolic Research, University of Buckingham, Hunter Street, Buckingham MK18 1EG, UK.. mary.board@buckingham.ac.uk

SOURCE: European journal of pharmacology, (2000 Oct 6) Vol. 406, No. 1, pp. 33-40. Journal code: 1254354. ISSN: 0014-2999.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200012

ENTRY DATE: Entered STN: 22 Mar 2001  
Last Updated on STN: 22 Mar 2001  
Entered Medline: 7 Dec 2000

AB The beta(3)-adrenoceptor agonist, (RR+SS)-(+/-)-4-[2-(2-3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenoxyacetate (BRL37344), stimulated fuel utilisation by isolated mouse soleus muscle at concentrations 10- to 100-fold lower than those required to stimulate lipolysis in brown adipocytes. At 1x10<sup>-10</sup> M BRL37344, uptake and phosphorylation of 2-deoxyglucose was increased (40%), as was glucose-oxidation (50%), palmitate-oxidation (70%) and oxidation of [2-14C]pyruvate (2-fold), indicating stimulation of tricarboxylic acid cycle reactions. Oxidation of [1-14C]pyruvate was unaffected, indicating no stimulation of pyruvate dehydrogenase activity. Other beta(3)-adrenoceptor agonists, disodium(RR)-5-[2-[(2-(3-chlorophenyl)-2-hydroxyethyl)-amino]propyl]-1,3-benzodioxazole-2,2-dicarboxylate (CL316,243, 1x10<sup>-7</sup> M) and (S)-4-[2-[2-hydroxy-3-(4-hydroxyphenoxy)propylamino]ethyl phenoxy]methylcyclohexylphosphoric acid lithium salt (SB226552, 1x10<sup>-9</sup> M), achieved similar stimulation of 2-deoxyglucose uptake and phosphorylation but (+/-)-4-(3-t-butylamino-2-hydroxypropoxy)benzimidazol-2-one (CGP12177A) had no effect. The inhibitor of protein kinase A, H-89 (isoquinolinesulfonamide), had little effect on the stimulation of pyruvate-oxidation by BRL37344, while the specific inhibitor of protein kinase C, bisindolylmaleimide IX, reduced the stimulated rate to slightly below basal values. We consider that these responses provide evidence of the presence of a novel beta-adrenoceptor in skeletal muscle, which we have termed beta(skel)-adrenoceptor.

L7 ANSWER 6 OF 10 MEDLINE on STN DUPLICATE 4  
 ACCESSION NUMBER: 97259590 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 9105691  
 TITLE: Stimulation of cyclic AMP-dependent protein kinase in rat atria by (-)-CGP 12177 through an atypical beta-adrenoceptor.  
 AUTHOR: Kaumann A J; Lynham J A  
 CORPORATE SOURCE: Babraham Institute, Human Pharmacology Laboratory, Cambridge.  
 SOURCE: British journal of pharmacology, (1997 Apr) Vol. 120, No. 7, pp. 1187-9.  
 Journal code: 7502536. ISSN: 0007-1188.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199706  
 ENTRY DATE: Entered STN: 9 Jul 1997  
 Last Updated on STN: 9 Jul 1997  
 Entered Medline: 24 Jun 1997

AB Mammalian hearts possess an atypical beta-adrenoceptor (non-beta 1, non-beta 2, non-beta 3) through which (-)-4-(3-t-butylamino-2-hydroxypropoxy)benzimidazol-2-one ((-)-CGP 12177) causes cardiostimulant effects. Here we showed that (-)-CGP 12177 increased the activity of adenosine 3':5'-cyclic monophosphate (cyclic AMP)-dependent protein kinase in the presence of 200 nM (-)-propranolol in rat atria at a concentration (10 microM) that elicits maximum positive chronotropic and inotropic effects. The phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine (IBMX) potentiated the positive chronotropic and inotropic effects of (-)-CGP 12177. We suggest that the atypical beta-adrenoceptor is coupled positively to the Gs protein-adenylyl cyclase system.

L7 ANSWER 7 OF 10 MEDLINE on STN DUPLICATE 5  
 ACCESSION NUMBER: 95230578 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 7536246  
 TITLE: Agonist-independent, muscle-type-specific signal transduction pathways in cat esophageal and lower esophageal sphincter circular smooth muscle.  
 AUTHOR: Sohn U D; Han B; Tashjian A H Jr; Behar J; Biancani P  
 CORPORATE SOURCE: Department of Medicine, Rhode Island Hospital and Brown Medical School, Providence, USA.  
 CONTRACT NUMBER: DK 11011 (NIDDK)  
 DK 28614 (NIDDK)  
 SOURCE: The Journal of pharmacology and experimental therapeutics, (1995 Apr) Vol. 273, No. 1, pp. 482-91.  
 Journal code: 0376362. ISSN: 0022-3565.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199505

ENTRY DATE: Entered STN: 24 May 1995  
Last Updated on STN: 3 Mar 2000  
Entered Medline: 17 May 1995

AB Smooth muscle cells isolated from the circular muscle layer of cat esophagus and lower esophageal sphincter (LES) exhibit distinct contractile intracellular signal transduction pathways in response to acetylcholine. To determine whether these contractile pathways are muscle type dependent, the authors examined the signal transduction pathways utilized by substance P and bombesin, which in other tissues, use different signal transduction pathways, and by the GTP analog, guanosine 5'-O-3-thiotriphosphate (GTP gamma S), which activates all available G proteins. Western blot analysis of esophageal and LES circular muscle revealed the presence of Gq-G11 (42 kD), Gi1-Gi2 (40 kD) and Go-Gi3 (40 kD) types of G proteins. The responses of esophageal cells to bombesin and substance P were blocked by 1) a Gi3 protein antibody, 2) the inhibitor of specific phosphatidylcholine-phospholipase C (PLC) D609 potassium tricyclo-[5.2.1.0(2.6)]-decyl-(9[8])-xanthogenate, 3) inhibition of phosphatidic acid phosphohydrolase by propranolol, 4) the protein kinase C inhibitor 1-(5-isoquinolinesulfonyl)-2-methylpiperazine dihydrochloride (H7) and 5) incubation in Ca(++)-free medium. Conversely, the responses of LES muscle cells to bombesin and substance P were blocked by 1) a Gq-G11 antibody, 2) a phosphatidylinositol-specific PLC antagonist U-73122 (1-[6-[[17 beta-3-methoxyestra-1,3,5(10)-trien-17-yl]amino]hexyl]-1H-pyrrole-2,5-dione), 3) the calmodulin inhibitor CGS9343B (1,3-Dihydro-1-[(4-methyl-4H,6H-pyrrolo[1,2-a]-[4,1]benzoxazepin++ +-4 -yl)methyl-4-piperindinyl]-2H-benzimidazol-2-one maleate) and 4) incubation in Sr++. After permeabilization by saponin, inositol 1,4,5-trisphosphate contracted LES but not esophageal cells. The inositol 1,4,5-trisphosphate receptor antagonist heparin and depletion of intracellular Ca++ stores by thapsigargin or A23187 4- Benzoxazolecarboxylic acid, 5-(methylamino)-2-[[3,9,11-trimethyl-8-[1-methyl-2-oxo-2-(1H-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undec-2-yl)methyl]-, [6s-[6 $\alpha$  (2S\*,3S\*),8 $\beta$  (R\*), 9 $\beta$ , 11. alpha.]]-(9Cl), blocked bombesin- and substance P-induced contraction of LES but not of esophageal muscle. In addition, contraction in response to GTP gamma S, which activates all G proteins, was blocked in esophageal cells by a Gi3-protein antibody, propranolol, D609 and H7. In LES muscle cells, the response to GTP gamma S was blocked by a Gq protein antibody, U-73122 and CGS934B. These data demonstrate that, in esophageal muscle, different agonists activate the same Gi3 protein, phosphatidylcholine-specific phospholipases and protein kinase C-dependent pathway. (ABSTRACT TRUNCATED AT 400 WORDS)

L7 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1994:549410 CAPLUS Full-text

DOCUMENT NUMBER: 121:149410

TITLE: Mechanism of desensitization of the cloned vasopressin

V1a receptor expressed in Xenopus oocytes

AUTHOR(S): Nathanson, Michael H.; Burgstahler, Angela D.; Orloff, John J.; Mani, Arya; Moyer, M. Susan

CORPORATE SOURCE: Sch. Med., Yale Univ., New Haven, CT, 06510, USA

SOURCE: American Journal of Physiology (1994), 267(1, Pt. 1), C94-C103

CODEN: AJPHAP; ISSN: 0002-9513

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The vasopressin V1a receptor exerts its effects by G protein-mediated increases in cytosolic Ca<sup>2+</sup> (Cai<sup>2+</sup>) and activation of protein kinase C. The V1a receptor also undergoes autologous desensitization. To clarify the mechanism of this desensitization, the authors expressed the cloned receptor in Xenopus oocytes, and vasopressin-induced Cai<sup>2+</sup> waves were examined as an index of V1a activation using confocal microscopy. Pretreatment of oocytes with a minimal concentration of vasopressin inhibited further generation of Cai<sup>2+</sup> waves upon maximal stimulation. Such pretreatment did not abolish Cai<sup>2+</sup> waves induced by subsequent microinjection of inositol trisphosphate, suggesting that this phenomenon represents receptor desensitization rather than depletion of inositol trisphosphate-sensitive Cai<sup>2+</sup> stores. Pretreatment with phorbol dibutyrate, ionomycin, or 8-bromoadenosine 3',5'-cyclic monophosphate had no effect on vasopressin-induced Cai<sup>2+</sup> waves. Oocytes recovered from desensitization within 1 h, but the microtubule inhibitor (methyl-5-[2-thienylcarbonyl]-1H-benzimidazol-2-yl)carbamate (nocodazole) inhibited this recovery. Receptor binding sites were reduced by over 50% within 10 min of exposure to vasopressin, with no associated change in the K<sub>d</sub> for the V1a receptor. These findings indicate that 1) expression of the cloned V1a receptor in Xenopus oocytes, coupled with subcellular Cai<sup>2+</sup> imaging, provides a useful system to examine mechanisms of V1a desensitization, 2) the V1a receptor undergoes autologous desensitization in this exptl. system, and 3) protein kinase C, Cai<sup>2+</sup>, and cAMP do not appear responsible for this desensitization, but 4) microtubule-dependent recycling of the receptor is preserved in this system and may be important for receptor desensitization.

L7 ANSWER 9 OF 10 MEDLINE on STN  
 ACCESSION NUMBER: 91025129 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 2222519  
 TITLE: Modulation of doxorubicin-induced chromosomal damage by calmodulin inhibitors and its relationship to cytotoxicity in progressively doxorubicin-resistant tumor cells.  
 AUTHOR: Ganapathi R; Grabowski D; Hoeltge G; Neelon R  
 CORPORATE SOURCE: Division of Laboratory Medicine, Cleveland Clinic Foundation, OH 44195.  
 CONTRACT NUMBER: 2R01CA35531 (NCI)  
 SOURCE: Biochemical pharmacology, (1990 Oct 1) Vol. 40, No. 7, pp. 1657-62.  
 Journal code: 0101032. ISSN: 0006-2952.  
 PUB. COUNTRY: ENGLAND: United Kingdom  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199011  
 ENTRY DATE: Entered STN: 17 Jan 1991  
 Last Updated on STN: 3 Feb 1997  
 Entered Medline: 8 Nov 1990

AB Modulation of doxorubicin (DOX) cytotoxicity by the calmodulin inhibitor trifluoperazine (TFP) in progressively doxorubicin-resistant L1210 mouse leukemia cells is unrelated to effects on drug accumulation. Based on the clastogenic activity of DOX, the effects of TFP and the selective calmodulin inhibitor 1,3-dihydro-1-[1-[4-methyl-4H,6H-pyrrolo[1,2-a][4,1]-benzoxazepin-4-yl-methyl]-4-piperidinyl]-2H-benzimidazol-2-one(1:1) maleate (CGS9343B) on DOX-induced chromosomal damage and its relationship to cytotoxicity were evaluated in sensitive and progressively DOX-resistant L1210 cells. Potentiation of DOX cytotoxicity by CGS9343B (a potent inhibitor of calmodulin which does not inhibit protein kinase C) was related to the level of resistance. Further, for equivalent cytotoxicity, cellular DOX levels in the absence versus the presence of TFP or CGS9343B were markedly higher. Exposure to calmodulin inhibitors following DOX treatment enhanced chromosomal aberrations and cytotoxicity. Maximal effects of calmodulin inhibitors were apparent when used during and after DOX treatment, and potentiation of cytotoxicity was related to modulation of DOX-induced chromosomal aberrations. Results suggest that inhibition of calmodulin-regulated processes is a potential target in the modulation of DNA damage/repair, and could play a pivotal role in the expression of "acquired resistance" to DOX.

L7 ANSWER 10 OF 10 MEDLINE on STN  
 ACCESSION NUMBER: 87201466 MEDLINE Full-text  
 DOCUMENT NUMBER: PubMed ID: 3033469  
 TITLE: CGS 9343B, a novel, potent, and selective inhibitor of calmodulin activity.  
 AUTHOR: Norman J A; Ansell J; Stone G A; Wennogle L P; Wasley J W  
 SOURCE: Molecular pharmacology, (1987 May) Vol. 31, No. 5, pp. 535-40.  
 Journal code: 0035623. ISSN: 0026-895X.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 198706  
 ENTRY DATE: Entered STN: 3 Mar 1990  
 Last Updated on STN: 3 Mar 1990  
 Entered Medline: 18 Jun 1987

AB 1,3-Dihydro-1-[1-[(4-methyl-4H,6H-pyrrolo[1,2-a][4,1]-benzoxazepin-4-yl)methyl]-4-piperidinyl]-2H-benzimidazol-2-one (1:1) maleate was synthesized in six steps from methyl anthranilate and designated CGS 9343B. CGS 9343B inhibited calmodulin-stimulated cAMP phosphodiesterase activity with an IC50 value of 3.3 microm. CGS 9343B was 3.8 times more potent than trifluoperazine (IC50 = 12.7 microm) as an inhibitor of calmodulin activity. CGS 9343B did not inhibit protein kinase C activity at concentrations up to 100 microm, whereas trifluoperazine inhibited protein kinase C activity with an IC50 value of 43.9 microm. CGS 9343B weakly displaced [3H]spiperone from postsynaptic dopamine receptors with an IC50 value of 4.8 microm while the value for trifluoperazine, a potent antipsychotic agent, was 0.018 microm. It is concluded that CGS 9343B is a novel, potent, and selective inhibitor of calmodulin activity. Unlike trifluoperazine, CGS 9343B does

not inhibit protein kinase C activity and does not possess potential antidopaminergic activity.

=> s azaindol and kinase and inhibitor

L8 0 FILE MEDLINE

L9 6 FILE CAPLUS

TOTAL FOR ALL FILES

L10 6 AZAINDOL AND KINASE AND INHIBITOR

=> d ibib abs 1-6

L10 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:80698 CAPLUS Full-text

DOCUMENT NUMBER: 140:146173

TITLE: Preparation of pyrrolotriazines as selective VEGFR-2 and FGFR-1 kinase inhibitors for treatment of proliferative diseases

INVENTOR(S): Bhide, Rajeev; Ruel, Rejean; Thibeault, Carl; L'heureux, Alexandre

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 66 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

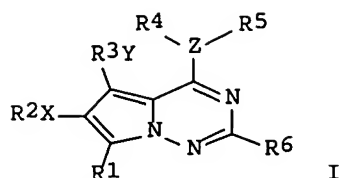
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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WO 2004009601	A1	20040129	WO 2003-US22554	20030718
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2492665	AA	20040129	CA 2003-2492665	20030718
AU 2003254017	A1	20040209	AU 2003-254017	20030718
US 2004063707	A1	20040401	US 2003-622593	20030718
US 6969717	B2	20051129		
US 2004072832	A1	20040415	US 2003-623171	20030718
US 6869952	B2	20050322		
EP 1539763	A1	20050615	EP 2003-765754	20030718
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
CN 1681818	A	20051012	CN 2003-821820	20030718
CN 1681508	A	20051012	CN 2003-821915	20030718
JP 2005538990	T2	20051222	JP 2004-523591	20030718
US 2005124621	A1	20050609	US 2005-35248	20050113
NO 2005000417	A	20050217	NO 2005-417	20050125
US 2006058304	A1	20060316	US 2005-214267	20050829
PRIORITY APPLN. INFO.:			US 2002-397256P	P 20020719
			US 2003-447213P	P 20030213
			US 2003-622593	A3 20030718
			US 2003-623171	A1 20030718
			WO 2003-US22554	W 20030718

OTHER SOURCE(S): MARPAT 140:146173

GI





AB Title compds. I [Z = O, S, N, etc.; X, Y = O, OCO, S, etc.; R1 = H, CH3, OH, etc.; R2, R3 = H, (un)substituted alkyl, alkenyl etc.; R4 = (un)substituted 7-azaindolyl, e.g., F, Cl, Me; R5 = H, absent when Z = O, S; R6 = H, (un)substituted alkyl, aryl, etc.] and their pharmaceutically acceptable salts were prepared. For example, electrophilic substitution of compound I [R1 = H; R2X = benzyloxy; R3Y = CH3; ZR5R6 = Cl] with 4-fluoro-5-hydroxy-7-azaindole, e.g., prepared from 4-chloro-1H-pyrrolo[2,3-b]pyridine in 6-steps, afforded compound I [R1 = H; R2X = benzyloxy; R3Y = CH3; ZR5R6 = 4-fluoro-7-azaindol-5-yloxy] in 80% yield. In VEGFR-2 and FGFR-1 kinase assays, 38-examples of compds. I exhibited IC50 values ranging from 0.001-10 µM. Of note, pyrrolotriazines I exhibited selective VEGFR-2 and FGFR-1 kinase inhibition (no data provided). Compds. I are claimed useful for the treatment of cancer, inflammation, autoimmune diseases.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:913164 CAPLUS Full-text

DOCUMENT NUMBER: 139:395805

TITLE: Substituted pyrroline kinase inhibitors, particularly 3-substituted-4-[1-(3-hydroxypropyl)-1H-pyrrolo[2,3-b]pyridin-3-yl]-1H-pyrrole-2,5-diones and analogs with activity against GSK-3 and PKC, and their preparation, pharmaceutical compositions, and use.

INVENTOR(S): Zhang, Han-Cheng; Kuo, Gee-Hong; Maryanoff, Bruce E.; Ye, Hong; O'Neill, David; Shen, Lan; Demarest, Keith; Conway, Bruce; Mccomsey, David F.

PATENT ASSIGNEE(S): Janssen Pharmaceutica N.V., Belg.

SOURCE: PCT Int. Appl., 155 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

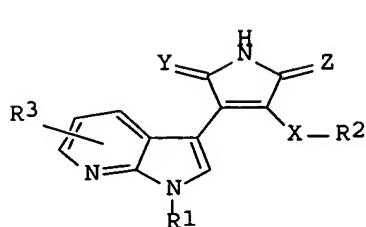
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

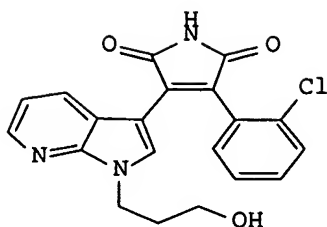
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003095452	A1	20031120	WO 2003-US14113	20030506
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2003225295	A1	20031111	AU 2003-225295	20030506
CA 2485527	AA	20031120	CA 2003-2485527	20030506
US 2004006095	A1	20040108	US 2003-430000	20030506
EP 1506192	A1	20050216	EP 2003-722017	20030506
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
JP 2005529918	T2	20051006	JP 2004-503468	20030506
PRIORITY APPLN. INFO.:			US 2002-378503P	P 20020508
			WO 2003-US14113	W 20030506

OTHER SOURCE(S): MARPAT 139:395805

GI



I



II

AB The invention is directed to novel substituted pyrroline compds., specifically compds. I, useful as kinase inhibitors, and methods for treating or ameliorating kinase-mediated disorders using I [wherein R1 = H, variety of sidechains containing ethers, amines, (hetero)aromatic rings, etc.; X = bond, alkyl, alkenyl, alkynyl; R2 = cycloalkyl, heterocyclyl, aryl, heteroaryl; or XR2 = cyano; R3 = H, 1-3 optional substituents; Y, Z = O, S, (H,OH), (H,H); provided that at least one of Y and Z is O]. Compds. I are especially useful as inhibitors of protein kinase C (including  $\alpha$ ,  $\beta$ -I,  $\beta$ -II, and  $\gamma$  isoforms) and glycogen synthase kinase 3 (including GSK-3 $\beta$ ). As such, I are claimed useful for treatment of a wide variety of cardiovascular diseases, diabetes and associated disorders, inflammatory diseases, immunol. disorders, dermatol. disorders, oncol. disorders, and CNS disorders. Approx. 80 compds. I and salts were prepared, and the free bases are claimed as a table. For instance, 7-azaindole was metalated with EtMgBr and acylated with ClCOCOMe to give RCOCOMe (R = 7- azaindol-3-yl). This compound was N1-alkylated with Br(CH<sub>2</sub>)<sub>3</sub>OSiMe<sub>2</sub>Bu-tert, then cyclocondensed with 2-ClC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>CONH<sub>2</sub> in the presence of KOBu-tert, and deprotected with HCl, to give title compound II. In tests against rabbit recombinant GSK-3 $\beta$ , II had IC<sub>50</sub> values of 0.009-0.010  $\mu$ M. Against isoenzymes of PKC at 1  $\mu$ M, II had inhibitions as follows:  $\alpha$  18%,  $\beta$ -II 14%, and  $\gamma$  48%.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 2001:851162 CAPLUS Full-text  
 DOCUMENT NUMBER: 136:6198  
 TITLE: Neuroprotective and anti-proliferative analogs of staurosporine and granulatimide, namely 3-(1H-indol-3-yl)-1H-pyrrole-2,5-diones, 3-(1H-indol-3-yl)-4-(1H-indol-1-yl)-1H-pyrrole-2,5-diones, and pyrrolo- $\beta$ -carboline derivatives, and their preparation and use as modulators of apoptosis  
 INVENTOR(S): Jaquith, James B.; Fallis, Alex; Gillard, John  
 PATENT ASSIGNEE(S): Aegera Therapeutics Inc., Can.  
 SOURCE: PCT Int. Appl., 95 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 2  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001087887	A2	20011122	WO 2001-CA718	20010518
WO 2001087887	A3	20020228		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,

BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2308994	AA	20011119	CA 2000-2308994	20000519
CA 2409355	AA	20011122	CA 2001-2409355	20010518
EP 1283836	A2	20030219	EP 2001-935858	20010518

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2004509068	T2	20040325	JP 2001-584281	20010518
US 2004220202	A1	20041104	US 2003-637599	20030811
US 2004102467	A1	20040527	US 2003-276803	20031023

PRIORITY APPLN. INFO.: CA 2000-2308994 A 20000519  
WO 2001-CA718 W 20010518

OTHER SOURCE(S): MARPAT 136:6198  
GI

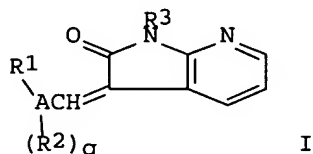
\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

AB The invention features 3-(1H-indol-3-yl)-4-(1H-indol-1-yl)-1H-pyrrole-2,5- diones of formula I, ring-substituted pyrrolo-β-carboline derivs. of formula II, and 3-(1H-indol-3-yl)-1H-pyrrole-2,5-diones of formula III, which are useful as neuroprotective and anti-proliferative compds. [wherein: A1, B1 = H, alkyl; A2, B2 = H, OH or ethers, SH or thioethers; or A1A2 or B1B2 = oxo; or B1B2 = thioxo in III; X1-3 = C, N; X4 = CH or N; only 0-2 of X1-4 = N; X5 = N, C, S, or CH; X6-8 = C, N; X9 = CH or N; only 0-2 of X6-9 = N; R1-3, R6-8 = lone pair or oxido when bound at X = N, otherwise = H, (un)substituted alkyl, halo, N3, cyano, NO2, NH2 or derivs., OH or derivs., SH or derivs., C.tplbond.CH or derivs.; R4, R5 = H, wide variety of linear and substituted sidechains, possibly including amino acid or sugar residues; or R4R5 form a ring; Y = H, halo, OH, or alkyl]. Also disclosed are methods for the preparation of these compds., selected biol. profiles and uses of these compds. in the treatment of various neurodegenerative and inflammatory diseases of the human nervous system, and in the treatment of various other proliferative disorders characterized by loss of growth or cellular differentiation control including, but not limited to, cancer and inflammation. Over 100 compds. were prepared and individually claimed. A variety of bioassays were performed on selected compds. For instance, 5-methoxyindole was treated with oxalyl chloride and then aqueous ammonium carbonate to give 5-methoxy-α-oxoindole-3-acetamide (IV). In a sep. reaction, indole was N-alkylated with BrCH2CO2Et using KOBu-text in THF, and the product was cyclized with IV in situ, to give title compound V. Cyclization of V using Me3SiOSO2CF3 in CH2Cl2 with concomitant oxidation over 3 days gave title compound VI. Both V and VI inhibited killing of mouse cerebral granule neurons by cisplatin in vitro, with an identical IC50 value of 10 μM. Biol. results suggest that the compds. prevent cell death by interfering with the apoptotic cascade at a point upstream of the caspases, i.e., the inhibition of one or several of the serine/threonine protein kinases directly upstream of the caspases. The compds. did not, however, significantly protect cancer cells from apoptosis. Furthermore, selected compds. down-regulated endogenous levels of HIAP1 mRNA in the neuroblastomal cell line LAN5, and thus represented new chemotherapeutics for treatment of cancer.

L10 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 1996:467094 CAPLUS Full-text  
 DOCUMENT NUMBER: 125:114586  
 TITLE: Preparation of substituted 3-arylidene-7-azaoxindoles  
 as tyrosine kinase inhibitors  
 INVENTOR(S): Buzzetti, Franco; Brasca, Gabriella Maria; Longo,  
 Antonio; Ballinari, Dario  
 PATENT ASSIGNEE(S): Pharmacia S.P.A., Italy  
 SOURCE: PCT Int. Appl., 58 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9616964	A1	19960606	WO 1995-EP4247	19951030
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

CA 2180730	AA	19960606	CA 1995-2180730	19951030
AU 9539262	A1	19960619	AU 1995-39262	19951030
EP 741726	A1	19961113	EP 1995-937030	19951030
EP 741726	B1	19991117		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
CN 1139929	A	19970108	CN 1995-191374	19951030
HU 74875	A2	19970228	HU 1996-2357	19951030
JP 09508924	T2	19970909	JP 1995-518113	19951030
AT 186727	E	19991215	AT 1995-937030	19951030
ES 2140717	T3	20000301	ES 1995-937030	19951030
ZA 9509927	A	19960610	ZA 1995-9927	19951122
US 5719135	A	19980217	US 1996-669315	19960709
NO 9603066	A	19960723	NO 1996-3066	19960723
FI 9602954	A	19960724	FI 1996-2954	19960724
GR 3032535	T3	20000531	GR 2000-400231	20000202
PRIORITY APPLN. INFO.:			GB 1994-23997	A 19941128
			WO 1995-EP4247	W 19951030
OTHER SOURCE(S):			CASREACT 125:114586; MARPAT 125:114586	
GI				



AB The preparation of substituted 3-arylidene-7-azaaxindoles I [A = benzene, naphthalene, 5,6,7,8-tetrahydronaphthalene, quinoline, isoquinoline, indole or 7-azaaxindole rings; R1 = H, CN, various sulfates and sulfonamides, CO2R6, CONHCH2(CHOH)nCH2OH, various amides, NR7R8, N(CH2CH2OH)2, NHCH2(CH(OH))nCH2OH, NHCONH2, NHC(NH2):NH, NHCO(CH(OH))nCH2OH, NHSO2R9, OR10, OCH2(CH(OH))nCH2OH, OOC(CH(OH))nCH2OH, OPO(OH)2, CH2NH2, C(NH2):NH, CH2NHC(NH2):NH, CH2OH, CH2OOC(CH(OH))nCH2OH, CH2OPO(OH)2, PO(OH)2, etc.; R2 is C1-6 alkyl, halo, or OH; R3 = H or C1-6 alkyl; R4 = H, C1-6 alkyl or CH2(CH(OH))nCH2OH; R5 = H, C1-6 alkyl, CH2(CH(OH))nCH2OH or (CH2)mNMe2; R6 = H, C1-6 alkyl or CH2(CH(OH))nCH2OH; each of R7 and R8 independently is H or C1-6 alkyl; R9 = Me or tolyl; R10 = H, C1-6 alkyl or C2-6 alkanoyl; Z = CH2, O, NH or NCH2CH2OH; n = 0, 1; m = 2, 3; p = 1-3; q = 0-2] are described, and their pharmaceutically acceptable salts, for use as tyrosine kinase inhibitors. A variety of processes are claimed for the preparation of I, including: (a) condensation of an aldehyde with an azaaxindole, (b) subjecting an amino-substituted 3-arylidene-7-azaaxindole to N-alkylation, N-acetylation, N-sulfonylation, N-amidation, or N-carbamoylation, (c) subjecting a hydroxy-substituted 3-arylidene-7-azaaxindole to O-alkylation, O-acylation, or O-phosphorylation, (d) esterification of a carboxy-substituted 3-arylidene-7-azaaxindole, (e) ammonia addition to a cyano-substituted 3-arylidene-7-azaaxindole, and (f) amination of a chloromethyl-substituted 3-arylidene-7-azaaxindole. As an example of the condensation reaction, 7-azaaxindole was refluxed with 3,5-di-tert-butyl-4-hydroxybenzaldehyde in EtOH with added piperidine for 3 h to give 3-[(3,5-di-tert-butyl-4-hydroxyphenyl)methylene]-7-azaaxindole in 80% yield. Another compound, 3-[(7-azaaxindol-3-yl)methylene]-7-azaaxindole, exhibited inhibitory activity for the in vitro p45 v-abl kinase assay (IC50 = 1.05 μM) and for the in vivo human chronic myeloid leukemia K562 cell growth inhibition assay (IC50 = 3.89). Pharmaceutical formulations of compds. I are claimed (2 examples).

L10 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 1996:209666 CAPLUS Full-text  
 DOCUMENT NUMBER: 124:260834  
 TITLE: Preparation and formulation of substituted

azaaxindolylidene compounds as tyrosine kinase inhibitors

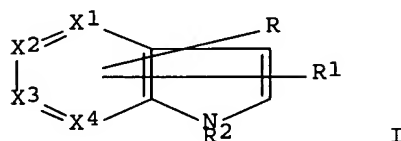
INVENTOR(S): Buzzetti, Franco; Brasca, Gabriella Maria; Longo, Antonio; Ballinari, Dario

PATENT ASSIGNEE(S): Pharmacia S.P.A., Italy

SOURCE: PCT Int. Appl., 64 pp.  
 CODEN: PIXXD2

DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9600226	A1	19960104	WO 1995-EP2043	19950530
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2168659	AA	19960104	CA 1995-2168659	19950530
AU 9526716	A1	19960119	AU 1995-26716	19950530
EP 715628	A1	19960612	EP 1995-921777	19950530
EP 715628	B1	20021002		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
CN 1129941	A	19960828	CN 1995-190567	19950530
HU 74609	A2	19970128	HU 1996-729	19950530
JP 09502457	T2	19970311	JP 1995-502741	19950530
AT 225348	E	20021015	AT 1995-921777	19950530
PT 715628	T	20030228	PT 1995-921777	19950530
ES 2186721	T3	20030516	ES 1995-921777	19950530
JP 3773257	B2	20060510	JP 1996-502741	19950530
ZA 9505223	A	19960131	ZA 1995-5223	19950623
US 5663346	A	19970902	US 1996-592297	19960209
FI 9600751	A	19960219	FI 1996-751	19960219
NO 9600713	A	19960222	NO 1996-713	19960222
PRIORITY APPLN. INFO.:				
			GB 1994-12719	A 19940624
			WO 1995-EP2043	W 19950530
OTHER SOURCE(S): MARPAT 124:260834				
GI				

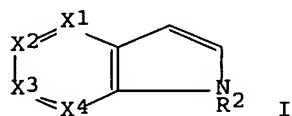


AB The title compds. I [one of X1, X2, X3, X4 is N and the others are CH; R is CH:C(CN)CONH2, etc.; R1 is hydrogen, amino, carboxy, cyano, etc.; R2 is H, C1-C6 alkyl, etc.; a proviso is given] are prepared 5-Cyano-3-[(7-azaindol-3-yl)methylen]-2-oxindole (NMR data given) in vitro showed IC50 of 0.98 mM against p-45 v-abl kinase.

L10 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2006 ACS on STN  
 ACCESSION NUMBER: 1994:557633 CAPLUS Full-text  
 DOCUMENT NUMBER: 121:157633  
 TITLE: Preparation and formulation of azaindoles as tyrosine kinase inhibitors  
 INVENTOR(S): Buzetti, Franco; Crugnola, Angelo; Ballinari, Dario; Greco, Felicita  
 PATENT ASSIGNEE(S): Farmitalia Carlo Erba S.R.L., Italy  
 SOURCE: PCT Int. Appl., 39 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9414808	A1	19940707	WO 1993-EP3536	19931215
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN,				

MW, NO, NZ, PL, RO, RU, SK, UA, VN  
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE  
CA 2126228 AA 19940707 CA 1993-2126228 19931215  
AU 9458105 A1 19940719 AU 1994-58105 19931215  
AU 670488 B2 19960718  
EP 626963 A1 19941207 EP 1994-903774 19931215  
EP 626963 B1 19990609  
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE  
HU 67431 A2 19950428 HU 1994-1950 19931215  
JP 07504208 T2 19950511 JP 1994-514761 19931215  
JP 3507497 B2 20040315  
AT 181074 E 19990615 AT 1994-903774 19931215  
ES 2134926 T3 19991016 ES 1994-903774 19931215  
IL 108087 A1 19970930 IL 1993-108087 19931220  
ZA 9309578 A 19940811 ZA 1993-9578 19931221  
CN 1093707 A 19941019 CN 1993-112970 19931222  
US 5397787 A 19950314 US 1993-171154 19931222  
FI 9403838 A 19940819 FI 1994-3838 19940819  
PRIORITY APPLN. INFO.: GB 1992-26855 A 19921223  
WO 1993-EP3536 W 19931215  
OTHER SOURCE(S): MARPAT 121:157633  
GI



AB Title compds. [I; R2 = H, alkyl, alkanoyl; 1 of X1-X4 = N and the others are CH; any C may be substituted by R or R1; R = CH:C(CN)R6, (un)substituted 2-oxo-3-indolyldenemethylene; R1 = H, halo, alkyl(oxy), NO2, (di)(alkyl)amino; R6 = CONH2, CONH(CH2)nPh, CSNH2, cyano; n = 0-5] were prepared Thus, 7-azaindole was formylated and the product refluxed with 2-oxindole in EtOH containing piperidine to give (Z)-3-[(7-azaindol-3-yl)methylene]-2-oxindole which had IC50 of 0.05  $\mu$ M against p45 v-abl kinase in vitro.

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